Attachment B: Literature Review

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Arnold J, Sarks S / Age-related macular degeneration / British Medical Journal / 2000	Review	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article reviewed the scientific evidence on treatments for age-related macular degeneration (AMD). However, no direct clinical evidence was presented.
Bressler N / Macular degeneration and related disorders / Practical Atlas of Retinal Disease and Therapy, Second Edition / 1997	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provided an overview of the clinical features and etiology of AMD. In addition, the article discussed treatments that are currently available. However, no direct clinical evidence was presented.
Bressler N, Brown G, Flynn H, Marmor M, Anderson L, Grand M / Photocoagulation and photodynamic therapy / American Academy of Ophthalmology's Basic Clinical Skills Course Section 12 / 2000	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provided an overview of laser photocoagulation therapy and ocular photodynamic therapy (OPT) in the treatment of AMD. However, no direct clinical evidence was presented.
Bressler N, Brown G, Flynn H, Marmor M, Anderson L, Grand M / Retina and vitreous / American Academy of Ophthalmology's Basic Clinical Skills Course Section 12 / 2000	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provided an overview of the clinical features and etiology of AMD. In addition, the article discussed current treatments. However, no direct clinical evidence was presented.

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Bressler N, Gragoudas E, Bressler S / Age-related macular degeneration, chapter 138: choroidal neovascularization / Principles and Practice of Ophthalmology / 1993	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provided a useful overview on the physiology and etiology of "wet" AMD.
Bressler S, Gragoudas E, Bressler N / Age-related macular degeneration, chapter 137: drusen and geographic atrophy / Principles and Practice of Ophthalmology / 1993	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provided a useful overview on the physiology and etiology of "dry" AMD.
Fine S / Photodynamic therapy with verteporfin is effective for selected patients with neovascular age-related macular degeneration / Archives of Ophthalmology / 1999	Editorial	Not a clinical trial	Not a clinical trial	Not a clinical trial	Article discussed OPT with verteporfin and appropriate patient populations that should receive it. Author states that OPT should be used on patients with classic CNV rather than occult CNV. Author also mentions the Verteporfin in Photodynamic Therapy Trial (VIP Trial) that is currently being conducted to examine whether or not those with occult CNV would benefit from OPT with verteporfin.

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Fine S, Berger J, Maguire M, Mauren G, Ho A / Age-related macular degeneration / New England Journal of Medicine / 1999	Review	Not a clinical trial	Not a clinical trial	Not a clinical trial	Article provided an overview of the clinical features and etiology of AMD. In addition, article reviewed the scientific evidence on current treatments and discussed possible future treatments being investigated. However, no direct clinical evidence was presented.
Hartnett M / Age-related macular degeneration / Medicine for the Practicing Physician: 4th Edition / 1996	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provided an overview of the clinical features and etiology of AMD. In addition, article discussed current treatments. However, no direct clinical evidence was presented.
Loewenstein A, Bressler N, Bressler S / Epidemiology of age-related retinal pigment epithelial disease / Retinal Pigment Epithelium: Current Aspects of Function and Disease / 1998	Review	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provided a review of several epidemiological studies conducted to assess the prevalence of AMD. However, no direct clinical evidence was presented.

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Miller J, Schmidt-Erfurth U, Sickenberg M, et al / Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of a single treatment in a phase 1 and 2 study / Archives of Ophthalmology / 1999	Non-randomized, phase 1/2 clinical trial	Outcome measures used to assess short-term efficacy and safety were the extent of fluorescein leakage from the CNV (classic and occult), and the stabilization of best-corrected visual acuity at 12-week follow-up compared to baseline. Patients were assigned to one of 5 regimens: Regimen 1 = light dose of 50, 75, 100, 150 J/cm applied 30 minutes after infusion. Regimen 2 = light dose of 100 J/cm applied 20 minutes after infusion. Regimen 3 = light dose 50, 75, 100, 150 J/cm applied 30 minute after infusion. Regimen 4 = light dose of 50, 75, 100 J/cm applied 15 minutes after infusion. Regimen 5 = light dose of 12.5, 25, 50 J/cm applied 10 minutes after infusion.	128 patients with subfoveal CNV secondary to AMD were enrolled. Main inclusion criteria: clinical signs of CNV from any cause; CNV under the geometric center of the foveal avascular zone (subfoveal), some classic CNV (occult CNV could, but need not be present); best corrected visual acuity of 20/40 or worse; >=50 years of age. Main exclusion criteria: tears of RPE at screening; substantial hepatic, renal, or neurologic disease, additional retinovascular diseases compromising visual acuity of study eye; central serous retinopathy.	Mean visual acuity changes for the 5 regimens: 1 -0.2 (-3 to +2) 2 -0.9 (-9 to +5) 3 -1.6 (-9 to +2) 4 +0.4 (-8 to +7) 5 +0.1 (-8 to +9) Regimen 2 & 3 caused marked vision loss. Cessation of leakage was noted in all regimens by 1 week after initial treatment. OPT with verteporfin achieved short-term cessation of fluorescein leakage without the loss of vision or growth of classic CNV lesion in some patients with AMD.	This phase 1/2 clinical trial was a precursor to the TAP study. Study provides initial safety data for OPT with verteporfin. Study alone does not contain sufficient evidence to demonstrate the effectiveness of the treatment.

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Schmidt-Erfurth U, Miller J, Sickenberg M, et al / Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of retreatments in a phase 1 and 2 study / Archives of Ophthalmology / 1999	Non-randomized, phase 1/2 clinical trial	Extent of CNV leakage and changes in visual acuity of at least 3 lines. Criteria for retreatment or reenrollment: (1) evidence of leakage from classic or occult CNV, (2) greatest linear dimension of leakage less than 6400 micrometers, (3) no adverse event due to previous OPT, and (4) no other additional ocular abnormalities associated with visual loss. Reenrollment also requires leakage from classic CNV. Regimen 2 = light dose of 100 J/cm applied 20 minutes after infusion. Regimen 4 = light dose 50, 75, 100 J/cm applied 15 minute after infusion.	36 patients were divided into two protocols: (1) patients underwent retreatment 2-4 weeks after initial OPT treatment (n=31). (2) patients had participated in a single-treatment regimen and were reenrolled in a retreatment protocol sometime between 12 weeks and 6 months. Up to 3 additional courses of treatment were instituted if indicated at 4-week interval (n=5). Inclusions/exclusion criteria similar to Miller J, et al. 1999.	For patients in the first protocol, the average visual acuity change at the follow-up (16-20 weeks after initial treatment) was +0.2 lines (range -4 to +4 lines) in regimen 2, and -1.0 line (range -5 to +3 lines) in regimen 4. Similar outcomes were observed for the 5 reenrolled patients. Leakage reappeared by 4 to 12 weeks after retreatment in almost all cases. However, leakage activity appeared to be reduced after multiple OPT course.	This phase 1/2 clinical trial was a precursor to the TAP study. Study provides initial safety data for OPT with verteporfin. Study alone does not contain sufficient evidence to demonstrate the effectiveness of the treatment.

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Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group / Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials--TAP report 1 / Archives of Ophthalmology / 1999	Double-masked, randomized clinical trial	To determine whether OPT with verteporfin can safely reduce the risk of vision loss in patients with subfoveal choroidal neovascularization (CNV) caused by AMD. Primary efficacy outcome: the proportion of eyes that had fewer than 15 letters lost (approximately <3 lines of visual acuity loss) compared with the baseline 1 year after study entry. Secondary efficacy outcomes were: (1) the proportion of eyes that had fewer than 30 letters lost (approximately <6 lines of visual acuity loss) compared with baseline, (2) mean changes in contrast threshold, and (3) angiographic outcomes (progression of CNV and size of lesion).	Inclusion Criteria: - CNV due to AMD - Subfoveal CNV - Evidence of classic CNV - Area of CNV at least 50% of the area of the total neovascular lesion - lesion < or = to 5400 micrometers - Visual acuity 20/40 - 20/200 - At least 50 years of age - Provide informed consent Exclusion Criteria: - Tear (rip) of RPE - Other significant ocular diseases affecting vision in study eye - inability to obtain photographs to document CNV - History of treatment for CNV in study eye - Participation in another ophthalmic clinical trial or use of other investigative new drugs - Active hepatitis or liver disease - Porphyria or porphyrin sensitivity - Prior OPT for CNV - Intraocular surgery within 2 months or capsulotomy within last month 609 patients were enrolled; 402 patients were randomly assigned to verteporfin and 207 patients were assigned to placebo. The study was	94% of patients completed 12-month follow-up. The average number of treatments over one year was 3.4 treatments per patient for the verteporfin group and 3.7 treatments for the placebo group. At 1 year follow-up, 61.2% of entire verteporfin group compared with 46.4% in the placebo group lost fewer than 15 letters of visual acuity (P<.001). Mean loss in visual acuity was 2.2 letters in the verteporfin group and 3.5 in the placebo (p<.001). Loss of 30 letter or more was significantly lower in the verteporfin group compared to placebo (14.7 % vs. 23.7%). Patients in the experimental group experienced a stabilization in contrast sensitivity (with approximately 1 letter lost over 1 year). The placebo group gradually declined with an overall lost of 4.5 letters. Angiographic outcomes data reflected a significant improvement in CNV in patients treated with verteporfin compared to	This was a well-designed trial which is directly generalizable to the Medicare population. The efficacy outcomes were a relevant measure of patient visual functioning. Great lengths were taken to ensure study participants and the patients were masked to the treatment assignment, ensuring a minimal impact of selection bias on the study results. Lesion composition at baseline affected the magnitude of the treatment benefit to a significant degree. It appears that only patients with predominantly classic lesions (as defined by the protocol) benefit from verteporfin. Some questions still linger regarding the nature of the two trials described in this article. It is not certain whether the 2 trials under the TAP investigation can be considered separate and distinct if they are conducted under identical protocols. There was also no stratification of the data in regards to lesion composition which might

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			actually 2 multi-center clinical trials performed in 22 ophthalmology practices in Europe and North America. The baseline characteristics for the two randomly assigned groups were statistically balanced. Results based on 1 year of follow-up on an intent-to-treat basis. Patients were randomly assigned to treatment group using sealed envelopes. Extensive measures were taken so that patients, ophthalmologists, vision examiners, photographers, photograph graders, clinic monitors and sponsors were all masked to treatment assignments and results. Patients were given initial treatment of OPT and verteporfin. Follow-up examinations occurred every 3 months after initial treatment. At these exams, patients were retreated with the same regimen if angiography showed leakage.	placebo. Treatment benefit from verteporfin was limited to patients with predominantly classic CNV lesions (in which the area of classic CNV was >50% of the area of the entire lesion at baseline). For patients considered predominantly classic, there were significant differences between the two treatment groups in the portion of patients who experienced a visual acuity loss of 15 letters or more (33% vs. 61%, $p < .001$) Patients with 100% classic CNV benefited most from verteporfin therapy ($p < .001$). There were no significant differences in outcomes between placebo and verteporfin in patients that were considered minimally classic (in which the area of classic CNV is < 50% of the area of entire lesion).	help determine if there was a correlation between lesion composition and treatment benefit. Finally, the trial was compared to the natural history of AMD. There were no efficacy comparisons made to the current standard of treatment for AMD, photocoagulation therapy.

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Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group / Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials--TAP report 2 / Archives of Ophthalmology (in press) /	Follow-Up	See TAP report 1. Same efficacy outcomes as TAP report 1 at 2 years follow-up.	See TAP report 1.	87% of the verteporfin group and 86% of the placebo group completed the 24 month examination. During the second year, patients were retreated an average 2.2 times in the verteporfin group and 2.8 times in the placebo group. The benefits of verteporfin over placebo were sustained through the 2 year examination. 53% of the verteporfin group lost < 15 letters in visual acuity compared to 38% of the placebo group ($p < .001$). Where as contrast sensitivity remained stable for the verteporfin group (approx. 1.3 letters lost at both 12 and 24 months), the placebo group continued to decline (approx. 4.5 letters lost at 12 months and 5.2 letters lost at 24 months) ($p < .001$). The subgroup analysis indicated that treatment benefit continues to be limited to patients with predominantly classic lesions.	Article provides the results from the second year of follow-up for the TAP study. The data results show that the benefits of verteporfin observed during the first year of examination were sustained through 2 years of follow-up. In addition, the need for retreatment appears to have declined for both groups during the second year of follow-up. 24 months of follow-up continue to suggest that this therapy only benefits patients with predominantly classic lesions. Its is important to note that even the verteporfin group experienced a decline in visual acuity, though not as severe as the natural course of the disease. For additional comments, please refer to TAP report 1.